Clinical profile, long-term follow-up and outcome of juvenile systemic scleroderma: 25 years of clinical experience from North-West India

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ABSTRACT

Objective. *To describe the clinical profile, long-term follow-up and outcome of juvenile systemic scleroderma (JSSc) from a tertiary care referral hospital in North-West India.*

Methods. *A review of case records was performed and children with JSSc (disease onset <14 years of age) were analysed. Diagnosis was based on the Paediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for JSSc.*

Results. *Forty patients (28 girls and 12 boys; F:M ratio= 2.3:1) were diagnosed with JSSc (including 22 children with overlap) in the last 25 years. Mean age at symptom onset was 7.75±3.19 years with a mean delay in diagnosis of 2.275±2.09 years. Raynaud's phenomenon was seen in 26/40 (65%) patients at presentation. Lung involvement was noted in 40% patients. Methotrexate was the most commonly used therapy, followed by oral prednisolone. Patients without overlap had higher incidence of cutaneous ulcers as compared to patients with overlap (55% vs. 18%; p-value: 0.01). Patients with overlap required significantly higher oral prednisolone (81% vs. 22%), methotrexate (72% vs. 38%) and hydroxychloroquine (54% vs. 5%) while cyclophosphamide (13% vs. 44%) and azathioprine (9% vs. 44%) were used relatively less in this group. Mortality was 15% at a mean follow-up of 51.75 months. Infections were noted to be the most common cause of death. There was no significant difference in the mortality between patients with and without lung disease or patients with or without overlap.*

Conclusion. *We describe the largest single-centre cohort with longest follow-up of juvenile systemic scleroderma from India.*

Introduction

Juvenile systemic scleroderma (JSSc) is a multisystem connective tissue disease characterised by widespread skin fibrosis and internal organ involvement (1-4). Less than 5% cases of systemic scleroderma (SSc) have their onset in childhood and only a handful of studies report long term follow-up of SSc in childhood (4-15). JSSc is a rare disorder with an approximate incidence of <1 per million children (16). In this study, we analysed clinical and laboratory profile of a single-centre cohort of children with SSc from North-West India.

Patients and methods

This was a review of case records of children diagnosed with systemic scleroderma (disease onset <14 years of age) and followed-up at Paediatric Rheumatology Clinic, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Our institute is a not-for-profit tertiary care referral centre for North-West India. All children diagnosed to have JSSc between January 1994 and December 2018 were eligible for analysis if they fulfilled the Paediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for JSSc (1). Patients were classified as limited SSc when skin thickening was restricted to distal extremities (*i.e.* distal to elbows or knees) and/or face

while diffuse SSc was labelled when skin thickening involved upper arms, thighs, anterior chest, or abdomen. Patients having overlap syndromes were also included in the analysis.

Modified Rodnan Skin Score (mRSS) was used to quantify severity of skin tightness (17) and juvenile systemic scleroderma severity score (J4S) (18) was used to assess severity of systemic disease. However, mRSS and J4S have only been administered during last 4 years and could not be assessed regularly in all patients.

Pulmonary function tests (PFT) included forced expiratory volume 1 (FEV1) and forced vital capacity (FVC). Restrictive pattern was classified as mild when FVC was between 70-80%; moderate, when FVC was between 60-70%; moderately severe, when FVC was between 50–60% and severe, when FVC was less than 50%. High-resolution computed tomography (HRCT) was carried out to assess pulmonary involvement in selected patients. HRCT chest was also repeated in some patients depending on clinical assessment. Indications included development of dyspnea on exertion, cough, crepitations on chest auscultation, clubbing or restrictive pattern on FVC. Routine follow-up CT was not performed in all patients. Echocardiography and 12-lead electrocardiography (ECG) were used to assess cardiac involvement. Pulmonary artery hypertension (PAH) was defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg.

Initially, patients were being referred to the Department of Dermatology in our institute for dermatoscopic evaluation of nail fold capillary changes. We have now been performing nail fold capillaroscopy (*Optilia Digital Capillaroscopy System*) ourselves since June 2018. However, nailfold capillaroscopy or dermatoscopy could not be performed in all patients and this assessment was not carried out routinely during follow-up.

Patients with gastrointestinal symptoms (dysphagia or reflux) were evaluated using either barium swallow studies or oesophageal manometry. Laboratory investigations included: complete blood count, renal function tests, urine examination and antinuclear antibody [ANA] (using indirect immunofluorescence method with 1:40 dilution and immunoblot to assess for antibodies against extractable nuclear antigen). Patients who had evidence of interstitial lung disease (ILD) were treated with injection cyclophosphamide pulses (500–750 mg/m^2/pulse) for 6–12 months followed by azathioprine (2–2.5 mg/kg/day) as maintenance therapy for a variable period of 2–5 years. Patients without any major organ disease were initiated on methotrexate (15–20 mg/m^2/week subcutaneous). Corticosteroids (oral prednisolone/intravenous methylprednisolone or intravenous dexamethasone) were also used in patients with glomerulonephritis, ILD, arthritis or

Table I. Clinical and laboratory manifestations in the study cohort.

Clinical manifestation	% (n=40)
Skin involvement	
Raynaud's phenomenon	40/40 (100%)
Skin tightness	40/40 (100%)
Calcinosis	10/40 (25%)
Telangiectasia	7/40 (17.5%)
Acro-osteolysis	4/40 (10%)
Digital gangrene	3/40 (7.5%)
Cutaneous ulcers (Fig. 1A)	14/40 (35%)
Lung involvement	16/40 (40%)
Dyspnea on exertion	4/40 (10%)
Abnormal pulmonary function test (Moderate to severe restriction)	10/32 (31.2%)
Abnormal CT chest	13/26 (50%)
Reduced DLCO	1 patient
PAH	5/40 (12.5%)
Gastrointestinal involvement	8/40 (20%)
Dysphagia	5/40 (12.5%)
Dilated oesophagus on CT	2 patients
Abnormal barium swallow	2 patients
Abnormal oesophageal manometry	2 patients
Cardiac involvement	
Tricuspid regurgitation	3/40 (7.5%)
Musculoskeletal involvement	
Arthritis	10/40 (25%)
Contractures leading to restriction of joint movements	16/40 (40%)
Positive antinuclear antibody (ANA)	34/39 (87.1%)
Speckled	15/39 (38.4%)
Nucleolar	8/39 (20.5%)
Diffuse	2/39 (5.1%)
Mixed speckled and nucleolar	3/39 (7.6%)
Mixed diffuse and nucleolar	4/39 (10.2%)
Cytoplasmic	1/39 (2.5%)
Cytoplasmic and nucleolar	1/39 (2.5%)
Antibodies against extractable nuclear antigen	15/18 (83.3%)
Anti U1RNP	5 patients
Anti Scl-70	3 patients
Anti SSA/Ro52	2 patients
Anti PMScl	2 patients
Anti Jo1	2 patients
Anti Sm	2 patients
Anti RiboP	1 patient
Anti PCNA	1 patient
Overlap syndrome	22/40 (55%)
SLE	8/22 (36.3%)
JDM1/22 (4.5%)	17/22 (77.2%)
PM	1/22 (4.5%)
JIA	6/22 (27.2%)
Lost to follow-up	6/40 (15%)
Mortality	6/40 (15%)

CT: computed tomography; DLCO: diffusion capacity of lung for carbon monoxide; JDM/PM: juvenile dermatomyositis/polymyositis; JIA: juvenile idiopathic arthritis; PAH: pulmonary artery hypertension; PCNA: proliferating cell nuclear antigen; RNP: ribonucleoprotein; Ribo P: ribosomal P; SLE: systemic lupus erythematosus.
*3 patients had only cutaneous signs of JDM and no clinical weakness or elevated muscle enzymes.

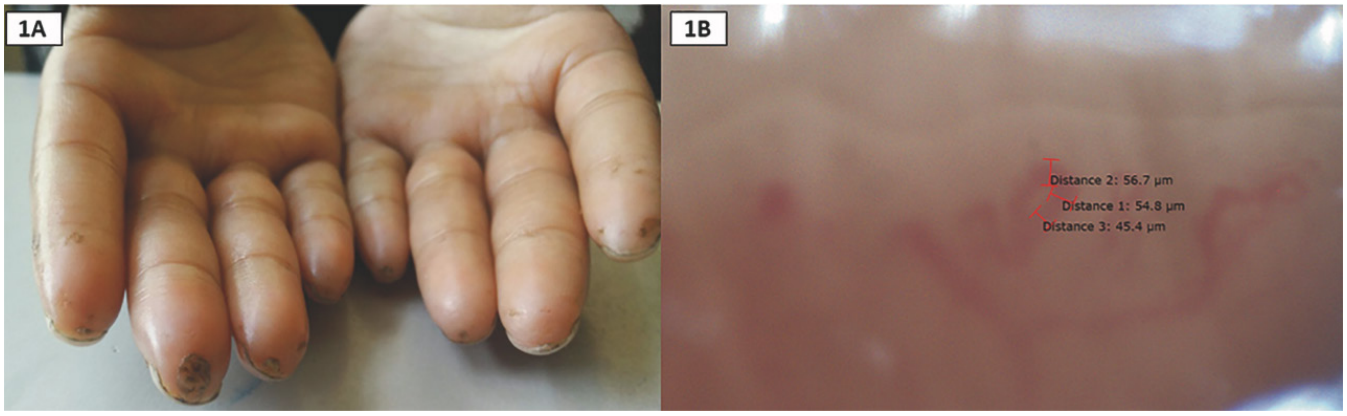

Fig. 1. Showing changes of peripheral vascular disease in patients with JSSc.
A. Digital tip ulcers in an 8-year-old boy with JSSc;
B. Nailfold capillaroscopy in a 12-year-old girl with JSSc showing active scleroderma pattern (giant capillaries, avascular areas and haemorrhages).

myositis. Raynaud phenomenon (RP) was managed using calcium channel blockers (nifedipine). Patients with rapidly progressing digital gangrene were also managed using endothelin receptor antagonists (bosentan) and prostaglandin E1 (alprostadil). Eight patients who were not coming for regular follow-up were contacted through telephone and/or letters. Two amongst these reported to the clinic while the remaining 6 were lost to follow-up.

Results

Forty patients (28 girls and 12 boys; F:M ratio= 2.3:1) were diagnosed with SSc (including 22 children with overlap) in last 25 years. Mean age at symptom onset was 7.75±3.19 years, while mean age at diagnosis was 10.02±2.48 years with a mean delay in diagnosis of 2.275±2.09 years. Clinical manifestations of patients are described in Table I. Of the 22 patients with overlap scleroderma, 8 had SLE, 17 had JDM, 6 had JIA and 1 had polymyositis. Eight of these patients in overlap scleroderma group had features suggestive of an overlap of more than 1 rheumatological disorder.

RP was noted in all patients and was recorded at presentation itself in 26/40 (65%) patients. RP was the sole presenting clinical manifestation in 20% of patients. Skin tightness as presenting symptom was noted in 26/40 (65%) patients while all 40/40 (100%) patients developed skin tightness at some point of their disease course. All patients had diffuse SSc.

Table II. Treatment details of all patients.

Treatment	% (n=40)
Oral prednisolone	22/40 (55%)
Intravenous methylprednisolone pulse	4/40 (10%)
Intravenous dexamethasone	2/40 (5%)
Methotrexate	23/40 (57.5%)
Cyclophosphamide pulses	11/40 (27.5%)
Azathioprine	10/40 (25%)
Mycophenolate mofetil	3/40 (7.5%)
Rituximab*	1/40 (2.5%)
Plasma exchange*	1/40 (2.5%)
Hydroxychloroquine	13/40 (32.5%)
Bosentan	2/40 (5%)
Alprostadil	1/40 (2.5%)

*Indication: diffuse alveolar haemorrhage

Skin biopsy was performed in 15 patients. It showed changes suggestive of scleroderma (thickened basement membrane, lymphomononuclear infiltration around capillaries, increased collagenisation in dermis) in all patients, non-specific inflammatory infiltrate in dermis in 1 and positive lupus band test in 1. Dermatoscopy or nail-fold capillaroscopy examination could be performed in 25 patients and showed variable abnormalities (tortuous and dilated capillary loops, capillary drop outs, avascular areas and haemorrhages) (Fig. 1B).

Lung involvement was seen in 16/40 (40%) patients. While 4 amongst these had dyspnea on exertion, others were detected when they were screened using PFT and/or CT chest. FVC revealed mild restriction in 14/40 (35%) patients; moderate/moderately severe restriction in 7/40 (17%) patients; and severe restriction in 3/40 (8%) patients. While majority of patients with abnormalities on CT chest had moderate to severe restriction on PFT (7/13, 53.8%), 4 had mild restriction and 2 had normal PFT. Moderate to severe restriction on PFT was observed in 10 patients – 7 amongst these had abnormalities on CT chest; in 2 CT was normal; CT could not be done in 1. Ground glass opacities and honeycombing were the commonest abnormalities found on CT chest. Majority of patients had abnormalities on CT at time of initial presentation (11/13, 84.6%), while 2 patients showed abnormalities on follow-up. One of these patients had normal imaging at baseline and developed ILD at 2 years of follow-up while he was on weekly methotrexate therapy. In this boy, FVC showed progressive worsening despite improvement in skin score. Repeat imaging, carried out at 2 years of follow-up, showed changes suggestive of ILD. Second patient had poor compliance to methotrexate therapy and presented

Table III. Comparison of clinical profile between patients with systemic sclerosis with and without features of overlap.

Clinical manifestations	SSc without overlap (n=18)	SSc with overlap (n=22)	*p*-value*
Mean age at onset of symptoms (years)	7.94 ± 3.17	7.59 ± 3.23	0.73
Mean age at diagnosis (years)	10.55 ± 2.81	9.59 ± 2.15	0.22
Mean delay in diagnosis (years)	2.61 ± 1.975	2 ± 2.18	0.36
Calcinosis	4/18 (22.2%)	6/22 (27.2%)	1
Sclerodactyly	15/18 (83.3%)	18/22 (81.8%)	1
Cutaneous ulcers	10/18 (55.5%)	4/22 (18.2%)	0.01
Lung involvement	9/18 (50%)	7/22 (31.8%)	0.33
PAH	3/18 (16.6%)	2/22 (9.1%)	0.15
Esophageal involvement	5/18 (27.7%)	3/22 (13.6%)	0.43
Myositis	0/18 (0%)	15/22 (68.2%)	0.000
Arthritis	3/18 (16.6%)	7/22 (31.8%)	0.27
ANA positivity	16/18 (88.8%)	18/21 (85.7%)	0.67
Treatment			
Oral prednisolone	4/18 (22.2%)	18/22 (81.8%)	<.001
Intravenous methylprednisolone pulse	1/18 (5.5%)	3/22 (13.6%)	1
Intravenous dexamethasone	1/18 (5.5%)	1/22 (4.5%)	1
Methotrexate	7/18 (38.8%)	16/22 (72.7%)	0.05
Cyclophosphamide pulses	8/18 (44.4%)	3/22 (13.6%)	0.03
Azathioprine	8/18 (44.4%)	2/22 (9.1%)	0.02
Hydroxychloroquine	1/18 (5.5%)	12/22 (54.5%)	0.001
Mortality	3/18 (16.6%)	3/22 (13.6%)	1

with progressive worsening of skin score and CT chest showed changes of ILD. Regression of ILD was also noted in 2 patients – at 2 years and 6 years of follow-up, respectively.

Treatment details for all patients are given in Table II. Methotrexate was the most commonly prescribed drug followed by oral prednisolone. Corticosteroids were predominantly used in patients with overlap syndromes for varied indications – glomerulonephritis, arthritis and myositis. However, these had to be initiated in 4 patients with diffuse SSc as well for ILD. Cyclophosphamide was the preferred modality for treatment of patients with ILD. Plasma exchange and rituximab were used in one patient because of diffuse alveolar haemorrhage. No other biological therapy was used and none of the patients was ever considered for haematopoietic stem cell transplant.

Six patients (15%) in our cohort died on follow-up. Cause of death was pneumonia in 2 patients (1 of them also had pneumothorax; while another one had *Streptococcus pneumoniae* positivity in blood culture) and diffuse alveolar haemorrhage in 1 patient (he also had overlap with SLE and lupus nephritis). One patient had sudden death at home possibly because of arrhythmia. She also had ILD that failed to respond to cyclophosphamide. Two patients died at home probably because of some infection (as per description given by parents) but exact cause could not be elucidated. None of the patients in this series died of progressive lung disease. Mean age at death was 14 years and mean duration of the disease before death was 6.1 years.

Duration of follow-up in our cohort is 2070 patient months with a mean follow-up of 51.75 months (±54.1, range 2–268). Six patients (15%) were lost to follow-up.

The clinical profile, treatment and outcome of patients with and without any

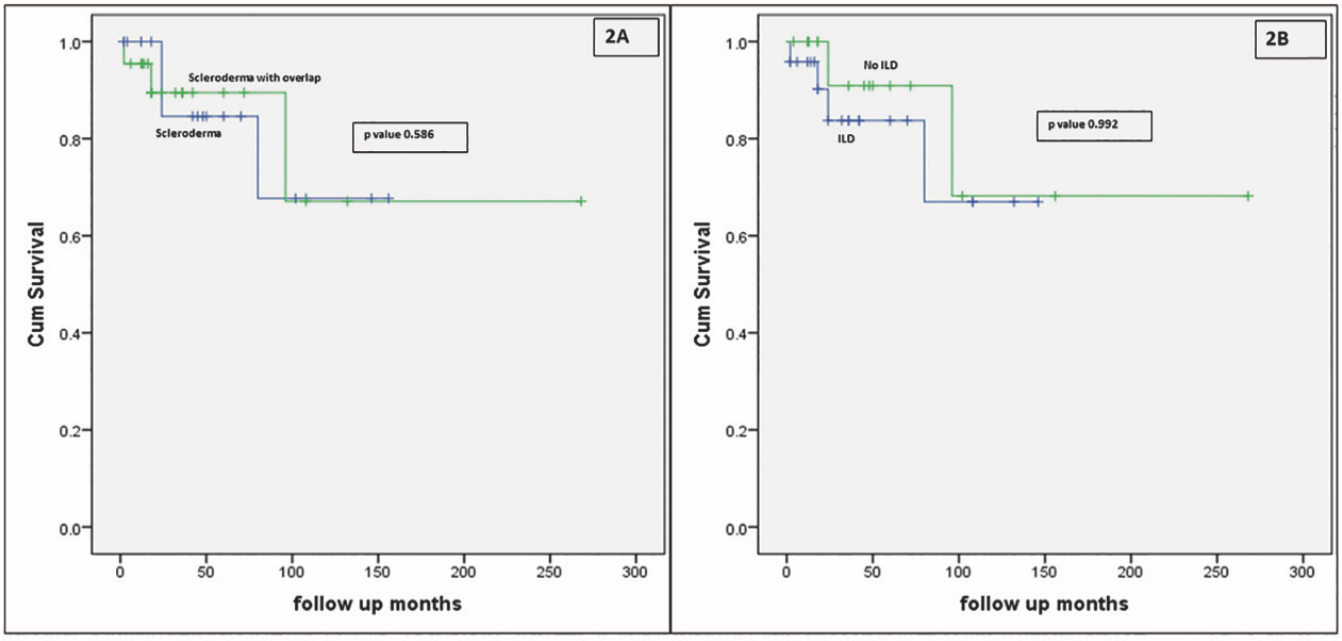

Fig. 2. Showing Kaplan-Meir survival curve in the study cohort.
A. Kaplan-Meir survival curve showing cumulative survival in patients with JSSc with and without overlap;
B. Kaplan-Meir survival curve showing cumulative survival in patients with JSSc with and without ILD.

features of overlap were compared. (Table III) There was no significant difference in mean age of symptom onset, mean age at diagnosis and mean delay in diagnosis between the 2 groups. Patients without overlap had higher incidence of cutaneous ulcers as compared to patients with overlap (55% *vs*. 18%; *p*-value: 0.01). Incidence of all other clinical manifestations and organ complications was comparable between the 2 groups (Table III). Patients with overlap were given significantly higher oral prednisolone (81% *vs*. 22%), methotrexate (72% *vs*. 38%) and hydroxychloroquine (54% *vs*. 5%) as compared to patients without overlap while cyclophosphamide (13% *vs*. 44%) and azathioprine (9% *vs*. 44%) was less frequently used in overlap group as compared to patients without overlap. There was no significant difference in mortality rate in the 2 groups. The Kaplan-Meier survival curve of 2 groups showed no statistically significant difference in the survival (*p*-value 0.586) (Fig. 2A). Similarly, there was no statistically significant difference in the survival curve of patients with or without ILD (*p*-value 0.992) (Fig. 2B). Clinical profile was compared between patients with scleroderma and mortality *versus* patients with scleroderma and no mortality (Table IV). There was no significant difference in the 2 groups except that significantly more patients in the first group were given methylprednisolone (33% *vs*. 5.9%, *p*-value 0.03).

Table IV. Comparison of clinical profile between patients with scleroderma and mortality *vs*. patients with scleroderma and no mortality.

Clinical manifestations	Patients with scleroderma and mortality (n=6)	Patients with scleroderma and no mortality (n=34)	*p*-value
Mean age at onset of symptoms (years)	8.16 (4.87-11)	8 (4.75-10.12)	0.84
Mean age at diagnosis (years)	10 (7.5-15.25)	10 (8-12)	0.75
Mean delay in diagnosis (years)	2 (0.87-4.87)	1.5 (1-2.25)	0.58
Calcinosis	0/6 (0%)	11/34 (32.3%)	0.10
Cutaneous ulcers	2/6 (33%)	14/34 (41.1%)	0.92
Lung involvement	2/6 (33%)	14/34 (41.1%)	0.71
PAH	2/6 (33%)	3/34 (8.8%)	0.10
Esophageal involvement	0/6 (0%)	8/34 (23.5%)	0.18
Myositis	3/6 (50%)	12/34 (35.3%)	0.49
Arthritis	2/6 (33%)	8/34 (23.5%)	0.60
ANA positivity	6/6 (100%)	28/34 (82.3%)	0.30
Treatment			
Oral prednisolone	5/6 (83%)	17/34 (50%)	0.13
Intravenous methylprednisolone pulse	2/6 (33%)	2/34 (5.9%)	**0.03**
Intravenous dexamethasone	0/6 (0%)	2/34 (5.9%)	0.54
Methotrexate	3/6 (50%)	20/34 (58.8%)	0.68
Cyclophosphamide pulses	3/6 (50%)	8/34 (23.5%)	0.18
Azathioprine	2/6 (33%)	8/34 (23.5%)	0.60
Hydroxychloroquine	2/6 (33%)	11/34 (32.3%)	0.96

Discussion

JSSc is a rare disorder with an estimated incidence of 0.27 cases per million children per year in the United Kingdom. Less than 5% of all SSc cases have onset in childhood (16, 19, 20). In this study we have analysed our cohort of 40 patients with JSSc collected over last 25 years from North-West India. The phenotype of several rheumatological disorders (such as JDM, SLE, Kawasaki disease and JIA) has been reported to be different in India when compared with the western literature (21-24). Moreover, the clinical presentation of SSc has been reported to be different in Asians (25). Therefore, it is important to study the phenotype of JSSc in India. To the best of our knowledge, the present study on 40 patients with JSSc is the largest reported single-centre cohort from any developing country.

Mean age at symptom onset (7.5 years) in our cohort was less as compared to several other series previously reported in the literature (8-14 years in different studies) (2, 5-15). It is possible that disease onset of JSSc in patients in North India is earlier than their counterparts in West. However, this remains a conjecture as our numbers are small. Further, the mean interval between onset of symptoms and diagnosis 2.275±2.09 years in our patients. This is much higher than figures reported from the Western countries (26, 27). This may represent lack of awareness about early clinical manifestations of JSSc amongst the referring paediatricians.

Proportion of patients with cutaneous clinical manifestations (RP, calcinosis, cutaneous ulcers and infarcts) reported in this series is similar to what has been reported previously (Table V).

ILD was seen in 40% of our patients. Reported incidence of ILD in JSSc has ranged from 9–92% (4, 6-15). Incidence of ILD seen in our study is much higher than one previously reported study from India (40% *vs*. 9%) (14). Better follow-up and active screening for evidence of ILD in some patients could be the reason for this apparent difference.

Gastrointestinal manifestations were seen in only 8 patients (20%). This figure is much lower than what has been reported previously (2, 4, 6, 8, 11-13, 15) (Table V). It may be noted that preemptive screening for gastro-oesophageal reflux was not carried out in our cohort.

Patients with JSSc may develop a variety of cardiac complications (28). In our series, we found PAH in 5 patients but none amongst these had cardiomyopathy or documented cardiac arrhythmia. We have screened for PAH using 2-D echocardiography. Cardiac catheterisation has not been carried out in any of our patients.

Neurological complications are rarely seen in patients with SSc (29). Only one patient in our series had neurological involvement in the form of seizures. Musculoskeletal involvement (arthralgia/arthritis) is commonly seen in patients with SSc (30). Patients may have restriction of joint movements because of tightness of skin around the joints. Approximately 10–15% patients may also develop myositis (31). We found arthritis in 25% patients, while 40% patients had restriction of joint movements because of skin tightness. Approximately 10–78% patients with

Table V. Review of published case series (including ≥10 patients) on juvenile systemic scleroderma.

Author/ Year/country	Number of patients; mean age at onset (years)	Raynaud at presentation (%)	Calcinosis (%)	Abnormal nail-fold capillaries (%)	Cutaneous ulcers and infarcts (%)	ILD (%)	GI involvement (%)	Cardiac involvement (%)	Neurological involvement (%)	Musculoskeletal involvement (%)	+ve ANA (%)	Overlap features (%)	Treatment	Mortality; median follow-up
Cassidy *et al*. 1977, USA (2)	15; NR	73	NR	NR	Pitting scar: 60	73	73	13	NR	Joint: 60 Muscle:27	57	46.6	CS	20%; NR
Garty *et al*. 1991, USA (4)	13; 6 (median)	69.2	NR	NR	NR	92.3	76.9	30.7	NR	53.8	NR	NR	NR	15.3; NR
Vancheeswaran *et al*. 1996, UK (5)	27; 11.7	81	NR	NR	NR	NR	NR	NR	NR	Limitation of joint movements: 100	37	NR	CS; CCB; d-penicillamine;	NR
Foeldvari *et al*. 2000, multi-national (6) 60 months (median)	135; 10.5	71.8	26.6	NR	NR	50.3	65	45	15.5	Joints- 78.5 Muscles- 9.6	5.1	NR	CS; MTX; HCQs; d-penicillamine	5.9%;
Martini *et al*. 2006, Multi-nation (7)	153; 8.1	83	19	40	29	29	Dysphagia in 24; GE reflux in 30	Pericarditis/ arrhythmia in 10; heart failure in 7	Seizures in 3, abnormal MRI in 3, peripheral neuropathy in 1	Arthritis 27, arthralgia 36, muscle weakness 24	80.7; ENA in 42.5%	Patients with overlap excluded	CS; MTX; Cyc; CCB; ACE inhibitors; PPI; d-penicillamine	11.8%; 30 months
Scalapino *et al*. 2006, USA (8)	111; NR	NR	NR	NR	NR	55	74	17	NR	82	97	29%	NR	37%; 206 months
Misra *et al*. 2007, India (9)	23; 13 (diffuse) 10 (limited) [Both median]	83	NR	NR	60.8 and 13 respectively	65.2	Dysphagia in 30.4; GE reflux in 34.7	NR		Arthritis in 34.7	65.2 excluded	Patients with overlap	CS; CCB; MTX; HCQs; Cyc; d-penicillamine; sildenafil	4.3%; 34 months (mean)
Foeldvari *et al*. 2010, Germany (10)	52; 14	100	NR	NR	NR	22	NR	3	NR	NR	75; ENA in 52%	37	CS; MTX; Cyc; Aza; MMF; cyclosporine; IVIg; ATG transplant;	27%; 108 months (mean)
Foeldvari *et al*. 2012, Multi-nation (11)	60; 12.2	95	NR	NR	35.6	23.3	Esophagus 60 Stomach 16.7 Intestine 15	PAH in 13.6	NR	Arthritis 10, contractures30, muscle weakness 20	90	9	NR	None; NR
Boroweic *et al*. 2012, Poland (12)	15; 8	86.7	NR	66.7	40	86*	46.7	*LV hypertrophy 20; LA enlargement 7; PAH 35; Wide IVC 23; AV block 7; Sinus tachycardia 14	NR	NR	60	NR	NR	7.3%; 123 months (mean)
Hatta *et al*. 2014, Japan (13)	11; 9.4	NR	9.1	NR	90.9	9.1	36.7	PAH 9.1	NR	Joint involvement 27.3	**	NR	NR	none;68.4 months (mean)
Bagri *et al*. 2017, India (14)	32; 9.4	68.7	NR	NR	18.7 and 3.7 respectively	9.3	9.3	NR	NR	Arthritis or arthralgia in 50, muscle weakness 31	50	31.2	CS; MTX; dexa; CCB; PPI; HCQs; sildenafil	None; 19.7 months
Stevens *et al*. 2018, USA (15)	64; 10.3	73	10	70	46	34	42	2	NR	Arthritis 19, contractures 34, myositis 12	84	6.2	CS; MTX; Cyc; Sulfasalazine; HCQs; MMF; IVIG; etanercept; abatacept	None; 14.52 months
Present study, India	40; 7.75 years	26/40 (65%)	10/40 (25%)	17/17 (100%)	Ulcers: 14/40 (35%), gangrene in 2/40 (5%)	40%	8/40 (20%)	PAH in 5/40 (12.5%)	1 patient had seizures	Arthritis in 10/40 (25%), restriction of joint movements due to tight skin 16/40 (40%)	34/39 (87.1%)	22/40 (55%)	CS; MTX; dexa; CCB; PPI; HCQs; Cyc; Aza; MMF sildenafil; Rituximab	6/40 (15%); 51.7 months (mean)

ACE: angiotensin convertase enzyme; ANA: antinuclear antibody; ATG: anti-thymocyte globulin; Aza: azathioprine; CCB: calcium channel blockers; CS: corticosteroids; Cyc: cyclophosphamide; dexa: pulse dexamethasone; ENA: extractable nuclear antigen; F/U: follow-up; GI: gastrointestinal; HCQs: hydroxychloroquine; ILD: interstitial lung disease; ??: inferior vena cava; IVIg: intravenous immunoglobulin; LA: left atrium; LV: left ventricular; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; MTX: methotrexate; NR: not reported; PAH: pulmonary artery hypertension; PPI: proton pump inhibitors.

*Probable referral bias as this study was carried out in a cardiology unit and patients were evaluated for specifically and extensively valuated for cardiovascular complications.

**Anti-topoisomerase 1 antibody in 90.9% and anti U1RNP in 9.1%.

JSSc have been reported to have arthritis (Table V).

ANA positivity was seen in 87% patients in our cohort. These results are similar to previously published data from other centres (Table V). It is known that approximately 6% patients of JSSc may be ANA negative (32). It has also been shown that ANA negative SSc patients constitute a different sub-group of the disease. They are more likely to be male, are at higher risk of gastrointestinal involvement and have lesser chances of cutaneous vasculopathy as compared to ANA positive SSc patients (33). None of the patients with ANA negativity in our series had gastrointestinal involvement, 2/5 (40%) had ILD and male to female ratio was 2:3.

Published literature of JSSc shows that JSSc overlap occurs in 6–46% of patients (Table V). Our results were largely similar, with overlap occurring in 55% patients. Common rheumatologic diseases that have been reported to have overlap with SSc include JDM, SLE, JIA or rheumatoid arthritis and primary Sjögren's syndrome (33, 34). No patient in the present study had primary Sjögren's syndrome.

A study by Foocharoen *et al*. compared the clinical profile of adult SSc patients with or without features of overlap (34). It was found that mean age of patients with features of overlap (16% of all patients in the cohort) was significantly less than patients with pure scleroderma. This may be one of the reasons for higher percentage of patients with overlap in the present study as ours was a paediatric cohort. It was also observed by Foocharoen *et al*. that patients with overlap syndrome required higher doses of steroids and were more frequently anti-topoisomerase I antibody positive (34). In our cohort, patients with overlap were similar in age of presentation and had significantly less incidence of cutaneous ulcers. Patients with overlap required significantly higher doses of oral prednisolone, methotrexate and hydroxychloroquine and significantly less cyclophosphamide and azathioprine as compared to patients with JSSc without overlap. No difference was observed in overall outcome in the 2 groups. Anti-topoisomerase I antibody was not positive in any of the 18 patients in whom this was tested. It may be important to carefully look at clinical features of other overlapping diseases with JSSc as this has been found to impact the therapeutic decisions (35).

Two patients in the present series had abnormal PFT (moderate restriction) but CT chest showed no abnormalities. There may be several reasons for this discrepancy. These include: 1. Fallacies in the interpretation of FVC values in young children (technical error); 2. False positivity for FVC in patients with SSc that could be because of tightening of skin of chest and abdominal wall; tightening of skin around the oral aperture and atrophy of accessory muscles (36-39).

Therapy used for treatment of our patients was largely similar to what has been used in the literature (Table V). However, we have not used cyclosporine, anti-thymocyte globulin (ATG) and biologics (except rituximab in 1).

Our study is the largest follow-up study on JSSc from India with a mean follow-up of 51.7 months (and total follow-up of 2070 patient months). Mortality rate of 15% in our cohort is higher than recently reported mortality in patients with SSc from various other centres (Table V) (11-15). Most common cause of death in children with JSSc is involvement of lungs, heart and kidneys. Reason for higher proportion of death in our series is likely because of late referrals, severe disease, infections and difficulty in accessing health care in emergency situations.

The main strength of our study is that this is the largest reported single-centre cohort of JSSc from India. We report a cumulative experience of 2070 patient months in JSSc. Being a single-centre study, there is uniformity in diagnosis. Despite having recorded ILD in more than 1/3rd of our patients, the overall prognosis has been reasonable.

There are a few limitations of this study. We could not perform regular assessments of disease activity using J4S and mRSS - a prospective longitudinal study with repeated assessments would have been more useful. Nail fold capillaroscopy assessment could not be performed in all patients at diagnosis and then at regular intervals to correlate with the disease activity. Six-minute walk test and diffusion capacity of lung for carbon monoxide (DLCO) was not carried out. We have not used biologics in any of our patients except rituximab in 1.

Conclusion

JSSc is a rare childhood rheumatic disease and limited form of SSc is even rarer in children. Overlap with other rheumatic diseases is more common in children with SSc as compared to adults. Children in our cohort were younger at disease onset as compared to many other previously reported cohorts. Even though mortality in patients with SSc has markedly reduced in last few years, infections would remain a significant concern in developing countries.

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